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(54) Title: COMPOUNDS USEFUL AS KINASE INHIBITORS FOR THE TREATMENT OF HYPERPROLIFERATIVE DISEASES

(57) Abstract: Novel kinase inhibitors and methods of using them are provided.



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**COMPOUNDS USEFUL AS KINASE INHIBITORS FOR THE
TREATMENT OF HYPERPROLIFERATIVE DISEASES**

FIELD OF THE INVENTION

The present invention relates to kinase enzyme inhibitors, pharmaceutical
5 compositions comprising these compounds and methods for identifying these compounds
and methods of using these compounds to treat various diseases including forms of cancer
and hyperproliferative diseases.

BACKGROUND OF THE INVENTION

Protein kinases play a critical role in the control of cell growth and differentiation,
10 and are key members of cellular signals leading to the production of growth factors and
cytokines. A partial non-limiting list of such kinases includes CDK2, CDK4, cdc2, CHK1,
CSBP/p38, EGF, Erb B2, Erb B3, Erb B4, FGF, Myt1, PDGF, PLK1, Tie, src, and wee-1
kinase.

Protein kinases play a critical role in the control of cell growth and differentiation
15 and are key mediators of cellular signals leading to the production of growth factors and
cytokines. See, for example, Schlessinger and Ullrich, *Neuron* 1992, 9, 383. A partial non-
limiting list of such kinases includes abl, ARaf, ATK, ATM, bcr-abl, Blk, BRaf, Brk, Btk,
CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, cfms, c-fms, CHK1,
c-kit, c-met, cRaf1, CSF1R, CSK, c-src, EGFR, ErbB2, ErbB3, ErbB4, ERK, ERK1, ERK2,
20 Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, Fps, Frk, Fyn, GSK,
gsk3a, gsk3b, Hck, IGF-1R, IKK, IKK1, IKK2, IKK3, INS-R, Integrin-linked kinase, Jak,
JAK1, JAK2, JAK3, JNK, JNK, Lck, Lyn, MEK, MEK1, MEK2, Myt1, p38, PDGFR, PIK,
PKB1, PKB2, PKB3, PKC, PKC α , PKC β , PKC δ , PKC ϵ , PKC γ , PKC λ , PKC μ , PKC ζ , PLK1,
Polo-like kinase, PYK2, src, tie1, tie2, TrkA, TrkB, TrkC, UL13, UL97, VEGF-R1, VEGF-
25 R2, wee-1, Yes and Zap70. Protein kinases have been implicated as targets in central
nervous system disorders such as Alzheimer's (Mandelkow, E. M. et al. *FEBS Lett.* 1992,
314, 315. Sengupta, A. et al. *Mol. Cell. Biochem.* 1997, 167,99), pain sensation (Yashpal,
K. *J. Neurosci.* 1995, 15, 3263-72), inflammatory disorders such as arthritis (Badger, *J.*
Pharm. Exp. Ther. 1996, 279, 1453), psoriasis (Dvir, et al, *J. Cell Biol.* 1991, 113, 857),
30 and chronic obstructive pulmonary disease, bone diseases such as osteoporosis (Tanaka et
al, *Nature*, 1996, 383, 528), cancer (Hunter and Pines, *Cell* 1994, 79, 573), atherosclerosis
(Hajjar and Pomerantz, *FASEB J.* 1992, 6, 2933), thrombosis (Salari, *FEBS* 1990, 263,
104), metabolic disorders such as diabetes (Borthwick, A.C. et al. *Biochem. Biophys. Res.*

Commun. 1995, 210, 738), blood vessel proliferative disorders such as angiogenesis (Strawn et al *Cancer Res.* 1996, 56, 3540; Jackson et al *J. Pharm. Exp. Ther.* 1998, 284, 687), restenosis (Buchdunger et al, *Proc. Nat. Acad. Sci USA* 1991, 92, 2258), autoimmune diseases and transplant rejection (Bolen and Brugge, *Ann. Rev. Immunol.* 1997, 15, 371) and infectious diseases such as viral (Littler, E. *Nature* 1992, 358, 160), and fungal infections (Lum, R. T. PCT Int. Appl., WO 9805335 A1 980212).

Entry into mitosis is initiated by the M phase-promoting factor (MPF), a complex containing the cdc2 protein kinase and cyclin B. Proper regulation of MPF ensures that mitosis occurs only after earlier phases of the cell cycle are complete. Phosphorylation of cdc2 at Tyr-15 and Thr-14 suppresses this activity during interphase (G1, S, and G2). At G2-M transition, cdc2 is dephosphorylated at Tyr-15 and Thr-14 allowing MPF to phosphorylate its mitotic substrates. A distinct family of cdc-regulatory kinases (Wee1) is known to be responsible for phosphorylation of the cdc Tyr-15. A new member of this family, Myt1, was recently described as the Thr-14 and Tyr-15-specific cdc2 kinase, and shown to be an important regulator of cdc2/cyclin B kinase activity (*Science* 270:86-90, 1995; *Mol. Cell. Biol.* 17:571, 1997). The inhibitory phosphorylation of cdc2 is important for the timing of entry into mitosis. Studies have shown that premature activation of cdc2 leads to mitotic catastrophe and cell death. Inhibition of Myt1 is predicted to cause premature activation of cdc2, and thus would kill rapidly proliferating cells. In addition, Myt1 inhibition is predicted to reduce resistance to conventional DNA-damaging chemotherapeutics, because the mechanisms by which cells avoid death involve arrest in the G2 phase of the cell cycle, and repair or DNA damage prior to division. That arrest should be prevented by blocking Myt1 inhibitory phosphorylation of cdc2. Thus forcing the cell to enter mitosis prematurely.

Myt1 kinase is an important cell cycle regulator, particularly at the G2/M phase. Inhibitors would therefore be attractive for the treatment of cancer. Current cancer therapies, including surgery, radiation, and chemotherapy, are often unsuccessful in curing the disease. The patient populations are large. For example, in colon cancer alone there are 160,000 new cases each year in the US, and 60,000 deaths. There are 600,000 new colon cancer cases each year worldwide. The number for lung cancer is twice that of colon cancer. The largest deficiency of chemotherapies for major solid tumors is that most patients fail to respond. This is due to cell cycle regulation and subsequent repair of damage to DNA or mitotic apparatus; the targets for most effective chemotherapeutic agents. Myt1 kinase offers a point of intervention downstream from these mechanisms by

which tumor cells develop resistance. Inhibition of Myt1 could in and of itself have therapeutic benefit in reducing tumor proliferation, and in addition, could be used in conjunction with conventional chemotherapies to overcome drug resistance.

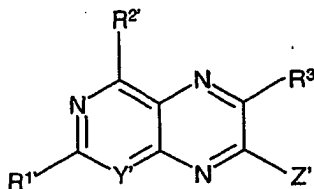
- Based on the foregoing, there is a need to identify potent kinase enzyme inhibitors for the treatment of various indications, including cancer, associated with the various receptors.

SUMMARY OF THE INVENTION

- The present invention involves compounds represented by Formula (I) hereinbelow, pharmaceutical compositions comprising such compounds, methods of antagonizing kinase receptors, and methods of treating diseases using these compounds.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of Formula (I) hereinbelow:



(I)

- wherein:

R^1 is selected from the group consisting of NRR^1 , OR, SR, SOR, SO_2R , and halo;

- R, R^1 , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, C_1 -alkyl, C_1 -alkanoyl, C_2 -alkenyl, C_2 -alkynyl, C_3 -10cycloalkyl, C_0 -3alkylaryl, C_0 -3alkylheterocyclyl, and C_0 -3alkylheteroaryl, wherein any of the foregoing carbon containing values may be optionally substituted by one or more of group A, on any position;

- A is selected from the group consisting of C_1 -alkyl, C_1 -alkanoyl, C_2 -alkenyl, C_2 -alkynyl, C_3 -10cycloalkyl, C_0 -3alkylaryl, C_0 -3alkylheterocyclyl, C_0 -3alkylheteroaryl, $C(=NH)R^2$, COR^2 , $CONR^2R^3$, $CON(O)R^2R^3$, $CONR^2R^3R^4Y$, CO_2R^2 , $C(O)SR^2$, $C(S)R^2$, cyano, trifluoromethyl, NR^2R^3 , $N(O)R^2R^3$, $NR^2R^3R^4Y$, NR^2COR^2 , $NR^2CONR^2R^3$, $NR^2CON(O)R^2R^3$, $NR^2CONR^2R^3R^4Y$,

NR²CO₂R², NR²C(O)SR², NR²SO₂R², NR²SO₂NR²R³, nitro, OR², OCF₃,
 aryloxy, heteroaryloxy, SR², S(O)R², S(O)₂R², SCF₃, S(O)CF₃, S(O)₂CF₃,
 SO₂NR²R³, SO₃R², PO₃R²R³, and halo, wherein C₁-galkyl, C₁-galkanoyl, C₂-
 galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl, C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl,
 5 (CH₂)₀₋₃heteroaryl, aryloxy, and heteroaryloxy are optionally substituted by one or
 more of group D, on any position;

Y is selected from an inorganic or organic anion;

D is selected from the group consisting of C₁-galkyl, C₁-galkanoyl, C₂-
 galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl, C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl, C₀₋₃
 10 3alkylheteroaryl, C(=NH)R², COR², CONR²R³, CON(O)R²R³, CONR²R³R⁴Y,
 CO₂R², C(O)SR², C(S)R², cyano, trifluoromethyl, NR²R³, N(O)R²R³,
 NR²R³R⁴Y, NR²COR², NR²CONR²R³, NR²CON(O)R²R³, NR²CONR²R³R⁴Y,
 NR²CO₂R², NR²C(O)SR², NR²SO₂R², NR²SO₂NR²R³, nitro, OR², OCF₃,
 aryloxy, heteroaryloxy, SR², S(O)R², S(O)₂R², SCF₃, S(O)CF₃, S(O)₂CF₃,
 15 SO₂NR²R³, SO₃R², PO₃R²R³, and halo, wherein C₁-galkyl, C₁-galkanoyl, C₂-
 galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl, C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl, C₀₋₃
 3alkylheteroaryl, aryloxy, and heteroaryloxy may be substituted by one or more of
 E, on any position;

R and R¹ together with the nitrogen to which they are attached and R¹⁴ and
 20 R¹⁵ together with the nitrogen to which they are attached may optionally and
 independently be N=CR²R³ or N=CR²NR²R³, and R¹ and R¹⁵ may optionally and
 independently be [hydrogen,]C(=NH)R², C(=NH)NR²R³, COR², C(S)R²,
 CONR²R³, CO₂R², C(S)NR²R³, SO₂R², SO₂NR²R³, or -[C=N(CH₂)₂₋₄(O)₀₋₁-
], and R and R¹ together with the nitrogen to which they are attached and R¹⁴ and
 25 R¹⁵ together with the nitrogen to which they are attached may optionally and
 independently may form a ring having 3 to 7 carbon atoms, optionally containing 1,
 2, or 3 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur,
 and nitrogen substituted with hydrogen, C₁-galkyl, or (CH₂)₀₋₃aryl;

R², R³, and R⁴ are independently selected from the group consisting of
 30 hydrogen, C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl,
 C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl, and C₀₋₃alkylheteroaryl; or R² and R³ taken

together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur, and nitrogen substituted with hydrogen, C₁-galkyl, or (CH₂)₀₋₃aryl, wherein any of the foregoing carbon
 5 containing values may be optionally substituted by one or more of group E, on any position;

E is selected from the group consisting of C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl, C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl, C₀₋₃alkylheteroaryl, C(=NH)R⁵, COR⁵, CONR⁵R⁶, CON(O)R⁵R⁶, CONR⁵R⁶R⁷Y,
 10 CO₂R⁵, C(O)SR⁵, C(S)R⁵, cyano, trifluoromethyl, NR⁵R⁶, N(O)R⁵R⁶, NR⁵R⁶R⁷Y, NR⁵COR⁵, NR⁵CONR⁵R⁶, NR⁵CON(O)R⁵R⁶, NR⁵CONR⁵R⁶R⁷Y, NR⁵CO₂R⁵, NR⁵C(O)SR⁵, NR⁵SO₂R⁵, NR⁵SO₂NR⁵R⁶, nitro, OR⁵, OCF₃, aryloxy, heteroaryloxy, SR⁵, S(O)R⁵, SO₂R⁵, SCF₃, S(O)CF₃, S(O)₂CF₃, SO₂NR⁵R⁶, SO₃R⁵, PO₃R⁵R⁶, and halo, wherein C₁-galkyl, C₁-galkanoyl, C₂-
 15 galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl, C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl, C₀₋₃alkylheteroaryl may be optionally substituted by one or more of a substituent selected from the group consisting of C(=NH)R⁵, COR⁵, CONR⁵R⁶, CON(O)R⁵R⁶, CONR⁵R⁶R⁷Y, CO₂R⁵, C(O)SR⁵, C(S)R⁵, cyano, trifluoromethyl, NR⁵R⁶, N(O)R⁵R⁶, NR⁵R⁶R⁷Y, NR⁵COR⁵, NR⁵CONR⁵R⁶, NR⁵CON(O)R⁵R⁶,
 20 NR⁵CONR⁵R⁶R⁷Y, NR⁵CO₂R⁵, NR⁵C(O)SR⁵, NR⁵SO₂R⁵, NR⁵SO₂NR⁵R⁶, nitro, OR⁵, OCF₃, aryloxy, heteroaryloxy, SR⁵, S(O)R⁵, SO₂R⁵, SCF₃, S(O)CF₃, S(O)₂CF₃, SO₂NR⁵R⁶, SO₃R⁵, PO₃R⁵R⁶, and halo, on any position;

R⁵, R⁶, and R⁷ are independently selected from the group consisting of hydrogen, C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl, C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl, and C₀₋₃alkylheteroaryl; or R⁵ and R⁶ taken
 25 together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, sulfur, or nitrogen substituted with hydrogen, C₁₋₆galkyl or (CH₂)₀₋₃aryl;

30 R^{2'} is selected from the group consisting of hydrogen, C₁-galkyl, COR⁸, CONR⁸R⁹, CO₂R⁸, cyano, trifluoromethyl, NR⁸R⁹, N(O)R⁸R⁹, NR⁸R⁹R¹⁰Y,

nitro, OR^8 , OCF_3 , SR^8 , S(O)R^8 , $\text{S(O)}_2\text{R}^8$, SCF_3 , S(O)CF_3 , $\text{S(O)}_2\text{CF}_3$,
 $\text{SO}_2\text{NR}^8\text{R}^9$, SO_3R^8 , $\text{PO}_3\text{R}^8\text{R}^9$, and halo;

R^8 , R^9 , and R^{10} are independently selected from the group consisting of
hydrogen, C_{1-8} alkyl, C_{1-8} alkanoyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-10} cycloalkyl,
5 C_{0-3} alkylaryl, C_{0-3} alkylheterocyclyl, and C_{0-3} alkylheteroaryl; or R^8 and R^9 taken
together with the nitrogen to which they are attached may optionally form a ring
having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected
from nitrogen, oxygen, sulfur, and nitrogen substituted with hydrogen, C_{1-8} alkyl, or
 $(\text{CH}_2)_{0-3}$ aryl;

10 $\text{R}^{3'}$ is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-}
gycloalkyl, aryl and heteroaryl, optionally substituted with one or more of group E,
cyano, CONHR^{11} , CONR^8R^9 , CO_2R^8 , NR^8R^9 , nitro, OR^8 , or halogen;

R^{11} is selected from the group consisting of 2-hydroxyethyl, 2-(C_{1-}
galkoxy)ethyl, or 2-($\text{R}^{12}\text{R}^{13}\text{N}$)ethyl;

15 R^{12} and R^{13} are independently hydrogen or C_{1-8} alkyl;

Y' is nitrogen or $\text{CR}^{2'}$;

Z' is $\text{NR}^{14}\text{R}^{15}$, OH , OR^{16} , SH , SR^{16} ; S(O)R^{16} ; SO_2R^{16} , or halo; and

R^{16} is selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-}
galkynyl, C_{3-10} cycloalkyl, C_{0-3} alkylaryl, C_{0-3} alkylheterocyclyl, and C_{0-}
20 C_{0-3} alkylheteroaryl, wherein any of the foregoing carbon containing values may be
optionally substituted by one or more of group E, on any position.

Preferred Y values include, but are not limited to, bisulfate, chloride,
fumarate, iodide, maleate, methanesulfonate, nitrate and sulfate.

Preferred compounds of the present invention are selected from the group
25 consisting of:

6-(2,6-Dichlorophenyl)-2-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-7-
methoxy-pteridine; and

3-(2,6-Dichlorophenyl)-7-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-2-
methoxy-pyrido[3,4-b]pyrazine;

30 and a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the present invention,

R^{1'} is NRR¹;

R is preferably hydrogen;

R¹ is C₀₋₃alkylaryl, preferably C₀alkylaryl, more preferably phenyl;

5 A is OR², preferably located at the 4-position;

R² is C₁₋₈alkyl, preferably ethyl substituted on the 2-position with E;

E is NR⁵R⁶, preferably substituted on the 2-position of R² = ethyl;

R⁵ and R⁶ are independently C₁₋₈alkyl, preferably ethyl;

R^{2'} is preferably hydrogen;

10 R^{3'} is aryl, preferably phenyl, optionally substituted with one or more of group E, wherein E is one or more of C₁₋₈alkyl, trifluoromethyl, or halo, preferably disubstituted at the 2,6-positions, more preferably 2,6-dichloro;

Z' is NR¹⁴R¹⁵ or OR¹⁶;

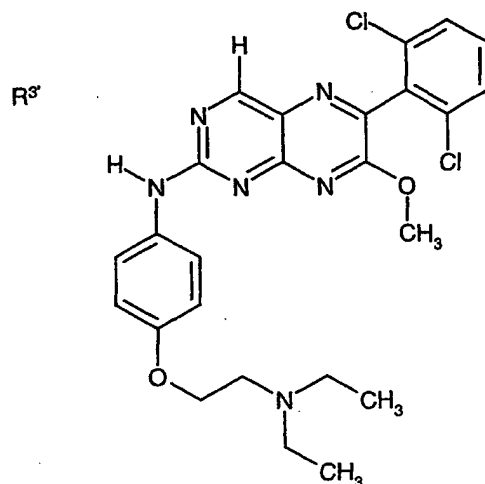
R¹⁴ and R¹⁵ are independently hydrogen or C₁₋₈alkyl;

15 R¹⁶ is C₁₋₈alkyl, preferably methyl; and

Y' is nitrogen or CR^{2'}; preferably Y' is nitrogen.

and a pharmaceutically acceptable salt thereof.

A particularly preferred embodiment of the present invention is:



20

wherein Z' is NH₂ or OCH₃, and a pharmaceutically acceptable salt thereof.

As used herein, the term "alkanoyl" is used herein at all occurrences to mean a C(O)alkyl group, wherein the alkyl portion is as defined below, including, but not limited to, acetyl, pivaloyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean a straight or branched chain radical, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

5 The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

 The term "alkyl" refers to a saturated hydrocarbon group joined together by single carbon-carbon bonds. The alkyl hydrocarbon group may be linear, or branched, including,
10 but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

 The term "alkylaryl" is used herein at all occurrences to mean a aryl group as defined below attached to an alkyl group as defined above, including, but not limited to, benzyl and phenethyl, and the like.

15 The term "alkylheterocyclyl" is used herein at all occurrences to mean a heterocyclic group as defined below attached to an alkyl group as defined above, including, but not limited to, (tetrahydro-3-furanyl)methyl and 3-(4-morpholinyl)propyl, and the like.

 The term "alkylheteroaryl" is used herein at all occurrences to mean a heteroaryl group as defined below attached to an alkyl group as defined above, including,
20 but not limited to, 3-(furanyl)methyl and (2-pyridinyl)propyl, and the like.

 The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical, wherein there is at least one triple bond between two of the carbon atoms in the chain, including, but not limited to, acetylene, 1-propylene, 2-propylene, and the like.

 The term "aralkyl" is used herein at all occurrences to mean an aryl moiety as
25 defined below, which is connected to an alkyl moiety as defined above, including, but not limited to, benzyl or phenethyl, and the like.

 The term "alkylaryl" is used herein at all occurrences to mean a aryl group as defined below attached to an alkyl group as defined above, including, but not limited to, benzyl and phenethyl, and the like.

30 The term "alkylheterocyclyl" is used herein at all occurrences to mean a heterocyclic group as defined below attached to an alkyl group as defined above, including, but not limited to, (tetrahydro-3-furanyl)methyl and 3-(4-morpholinyl)propyl, and the like.

The term "alkylheteroaryl" is used herein at all occurrences to mean a heteroaryl group as defined below attached to an alkyl group as defined above, including, but not limited to, 3-(furanyl)methyl and (2-pyridinyl)propyl, and the like.

5 The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical, wherein there is at least one triple bond between two of the carbon atoms in the chain, including, but not limited to, acetylene, 1-propylene, 2-propylene, and the like.

The term "aralkyl" is used herein at all occurrences to mean an aryl moiety as defined below, which is connected to an alkyl moiety as defined above, including,
10 but not limited to, benzyl or phenethyl, and the like.

The term "aryl" is used herein at all occurrences to mean 6-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to phenyl, naphthalenyl, biphenyl, phenanthryl, anthracenyl, and the like.

15 The term "aryloxy" is used herein at all occurrences to mean an aryl group as defined above linked via an oxy group, including, but not limited to, phenoxy, and the like.

The terms "cycloalkyl" is used herein at all occurrences to mean cyclic radicals, which may be mono- or bicyclo-fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-
20 tetrahydronaphthalenyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heteroaryl" is used herein at all occurrences to mean a 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-
25 cyclic systems, which ring or ring systems contain 1 to 4 heteroatoms selected from nitrogen, which may be optionally substituted with hydrogen or C₁-alkyl, oxygen, and sulfur, including, but not limited to, indolyl, benzofuranyl, thianaphthenyl, quinolyl, isoquinolyl, pyrrolyl, furanyl, thienyl, pyridyl, and the like.

The term "heteroaryloxy" is used herein at all occurrences to mean an heteroaryl
30 group as defined above linked via an oxy group, including, but not limited to, 2-pyridinyloxy, and the like.

The term "heterocyclic" is used herein at all occurrences to mean a saturated or wholly or partially unsaturated 5-10-membered ring system (unless the cyclic ring system

is otherwise limited) in which one or more rings contain one or more heteroatoms selected from nitrogen, which may be optionally substituted with hydrogen or C₁-alkyl, oxygen, and sulfur, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, 1,2,3,6-tetrahydropyridine, hexahydroazepine, and the like.

5 The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

10 The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

15 Geometric isomers and tautomers of the present compounds are also within the scope of the present invention.

 The present compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered.

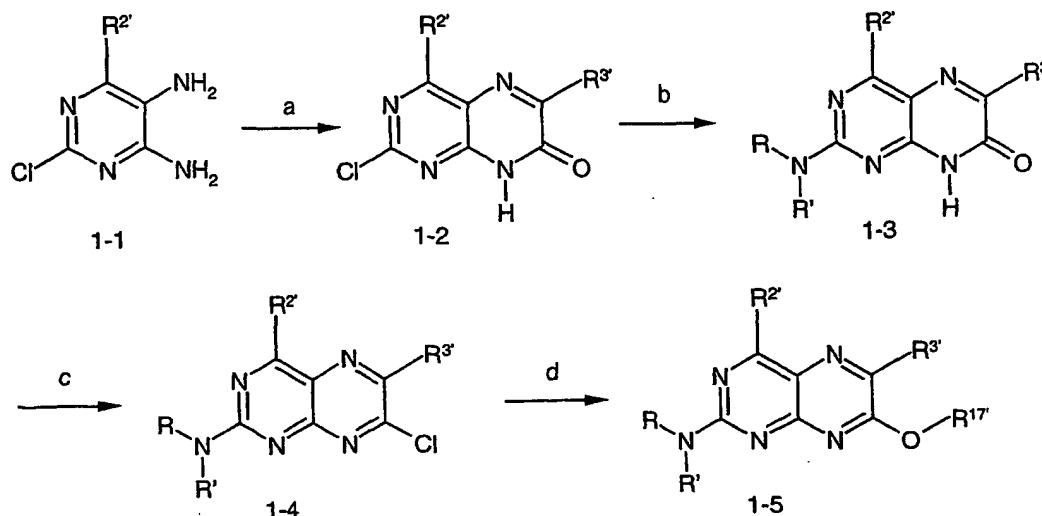
20 Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, 25 ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

 Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, 30 ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present.

 Preferred salts include sulfate, bisulfate, hydrochloride, fumarate, maleate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and sodium.

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

- 5 Specifically, compounds of formula (I) wherein Y' is nitrogen, R^{1'} is NRR¹, and R^{2'}, R^{3'}, and Z' are as defined for formula (I), are prepared by methods known to the art. Compounds of formula (I) can be prepared from appropriately substituted pyrimidine 1-1, which is commercially available or is prepared by methods known to the art. For example in Scheme 1, appropriately substituted 2-chloro-4,5-
- 10 diaminopyrimidine 1-1 is reacted with an appropriately substituted α -oxo carboxylic acid ester, for example ethyl α -oxobenzeneacetate, in an appropriate solvent, for example, water or ethanol, at an appropriate temperature, for example room temperature or reflux, to afford the substituted pteridin-7-ol 1-2.
- Treatment of 1-2 with a suitable amine, for example an appropriately substituted
- 15 alkyl amine or an appropriately substituted aniline, for example 4-[2-(diethylamino)ethoxy]aniline, with or without a suitable solvent, for example neat, at a suitable temperature, for example 150°C, for a suitable time, for example 1.5 hours, gives 1-3. Treatment of 1-3 with a suitable activating reagent, for example thionyl chloride, in a suitable solvent, for example chloroform, gives the chloro-
- 20 pteridine 1-4. Treatment of 1-4 with an appropriately substituted alcohol, for example methanol, and a suitable base, for example sodium hydride, at a suitable temperature, gives 1-5, a compound of formula (I) wherein Z' is OR¹⁶. Similarly, treatment of 1-4 with a appropriately substituted primary or secondary amine gives compounds of formula (I) wherein Z' is NR¹⁴R¹⁵.
- 25 Alternatively, the 2-chloro in 1-2 may be replaced by other suitable leaving groups such as alkylthio, for example methylthio, or alkylsulfinyl, for example methylsulfinyl.

Scheme 1:

(a) $\text{R}^3\text{COCO}_2\text{R}$, ethanol, Δ ; (b) RR^1NH , Δ ; (c) SOCl_2 , CHCl_3 ; (d) R^{16}ONa , R^{16}OH , Δ .

5

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above.

In order to use a present compound or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The present ligands can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and

redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art. The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50} , EC_{50} , the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula (I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

The present invention also provides compounds of formula (I) and pharmaceutically acceptable salts thereof (hereafter collectively referred to as the "active

compounds") for use in medical therapy, and particularly in the treatment of disorders mediated by a Kinase, such as Myt1 kinase.

A further aspect of the invention provides a method of treatment of a human or animal suffering from a disorder mediated by a protein kinase, said treatment comprising
5 administering an effective amount of an active compound of formula (I) to the human or animal patient.

In a related aspect the present invention comprises a method for inhibiting a kinase comprising bringing said kinase into contact with a compound of formula (I).

Another aspect of the present invention provides a method for using an active
10 compound of formula (I), in the preparation of a medicament for the treatment of malignant tumors, or for the treatment of disorders involving abnormal angiogenesis, such as arthritis, diabetic retinopathy, macular degeneration and psoriasis. Alternatively, compounds of formula (I) can be used in the preparation of a medicament for the treatment of a disease mediated by a kinase selected from the group consisting of: abl, ARaf, ATK, ATM, bcr-abl,
15 Blk, BRaf, Brk, Btk, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, cfms, c-fms, CHK1, c-kit, c-met, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, ERK1, ERK2, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, Fps, Frk, Fyn, GSK, gsk3a, gsk3b, Hck, IGF-1R, IKK, IKK1, IKK2, IKK3, INS-R, Integrin-linked kinase, Jak, JAK1, JAK2, JAK3, JNK, JNK, Lck, Lyn, MEK, MEK1, MEK2, Myt1, p38,
20 PDGFR, PIK, PKB1, PKB2, PKB3, PKC, PKC α , PKC β , PKC δ , PKC ϵ , PKC γ , PKC λ , PKC μ , PKC ζ , PLK1, Polo-like kinase, PYK2, src, tie1, tie2, TrkA, TrkB, TrkC, UL13, UL97, VEGF-R1, VEGF-R2, wee-1, Yes and Zap70.

Additionally, compounds of formula (I) can be used in the preparation of a medicament for the treatment of organ transplant rejection, tumor growth, chemotherapy-
25 induced mucositis, radiation-induced mucositis, plantar-palmar syndrome, chemotherapy-induced alopecia, chemotherapy-induced thrombocytopenia, chemotherapy-induced leukopenia and hirsutism or of treating a disease state selected from the group consisting of: mucocitis, restenosis, atherosclerosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, chronic
30 obstructive pulmonary disease, thrombotic microangiopathy, aglomerulopathy, psoriasis, diabetes mellitus, inflammation, a neurodegenerative disease, macular degeneration, actinic keratosis and hyperproliferative disorders.

Another aspect of the present invention provides the use of an active compound of formula (I), in coadministration or alternating administration with previously known anti-tumor therapies for more effective treatment of such tumors.

Another aspect of the present invention provides the use of an active compound of
5 formula (I) in the preparation of a medicament for the treatment of viral or eukaryotic infections.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease. As used herein, "diseases" treatable using the present compounds include, but are not limited to leukemias, solid tumor cancers,
10 metastases, soft tissue cancers, brain cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, lung cancer, bladder cancer, bone cancer, prostate cancer, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, kidney cancer, head cancer and neck cancer, chronic inflammatory proliferative diseases such as psoriasis and rheumatoid arthritis; proliferative cardiovascular diseases such as restenosis; proliferative ocular disorders such as
15 diabetic retinopathy; and benign hyperproliferative diseases such as hemangiomas.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a
20 flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a
25 hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound
30 or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

5 A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a
10 medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

15 The biological activity of the compounds of Formula (I) is demonstrated by the tests indicated hereinbelow.

In vitro assays:

Compounds capable of inhibiting Myt1 kinase can be identified with in vitro assays and cellular assays as described below. Variations of these assays would be obvious to
20 those skilled in the art. Additional assays for various protein kinases are provided in application WO 00/56710, incorporated herein in its entirety by reference.

Expression of GST-Myt1:

A GST-Myt1 expression construct was constructed which has the glutathione-S-transferase gene fused to the amino terminus of Myt1 kinase via a linker containing a
25 thrombin cleavage site. This clone has been truncated at amino acid 362 of Myt1, just prior to the to the transmembrane domain. This construct was cloned into the Baculovirus expression vector, pFASTBAC, and this was used to make the viral stock for the subsequent infection. Spodoptera frugiperda cells (Sf21) were infected with the virus expressing the GST-Myt1 and the cells were grown for 3 days, then harvested and frozen
30 down.

Purification of GST-Myt1:

The GST-Myt1 protein was purified as follows: An Sf21 cell pellet expressing GST-Myt1 was resuspended on ice in 10mls of lysis buffer (50mM Tris-Cl, pH 7.5, 250mM NaCl₂, 1mM dithiothreitol (DTT), 0.1%NP-40, 5% (v/v) protease inhibitor

- cocktail, 1mM sodium orthovanadate), cells were lysed by sonication and centrifuged at 100,000xg for 30min. The supernatant was added to 5mls (packed volume) of Glutathione Sepharose 4B, equilibrated in wash buffer (20mM Tris-Cl, pH 7.0, 10mM MgCl₂, 100mM NaCl₂, 1mM DTT, 0.5%(v/v) protease inhibitor cocktail, 1mM sodium orthovanadate).
- 5 The mixture was rocked for 30min. The resin with the bound GST-Myt1 was spun down at 500xg for 5min and washed with 14mls of wash buffer. The beads were spun as above and resuspended in another 14mls of wash buffer. The suspension was transferred into a column and allowed to pack, then the wash buffer was allowed to flow through by gravity. The GST-Myt1 was eluted from the column with 10mls of 10mM Glutathione in 50mM
- 10 Tris-Cl, pH 8.0 in 500ul fractions. Protein concentrations were determined on the fractions using Bio-Rad's Protein assay kit as per instructions. Fractions containing the GST-Myt1 were pooled and diluted to a concentration of ~0.5mg/ml and dialyzed for 4 hours at 4°C in dialysis buffer (20mM HEPES, pH 7.0, 1mM Manganese Acetate, 100mM NaCl₂, 0.05% Brij-35, 10% glycerol, 1mM DTT, 0.2% (v/v) protease inhibitor cocktail, 1mM sodium
- 15 orthovanadate). The protein was aliquoted and stored at -80°C.

Enzyme Assays:

GST-Myt1 autophosphorylation-DELFI assay

- Delayed fluorescent immunoassays (DELFI) were performed in 96well NUNC maxisorp plates, at 50ul/well with 0.25ug GST-Myt1, in BufferA (50mM HEPES, pH 7.4,
- 20 2mM Mn(OAc)₂, 5uM ATP, 1mM DTT). For determination of pH optimum, divalent cation usage and K_m of ATP, the appropriate component was varied as indicated in the figures. Autophosphorylation reactions were initiated by the addition of GST-Myt1 in buffer and were allowed to proceed at room temperature with shaking for 20min. The reactions were stopped with the addition of EDTA to a 20mM final concentration, and the
- 25 protein was allowed to continue to bind to the wells for an additional 40min. Wells were washed three times with 300ul TBS/Tween (50mM Tris, pH 7.4, 150mM NaCl₂, 0.2% Tween-20). After washing, the plate was blocked using Pierce's Superblock in TBS at 100ul/well. This was immediately decanted and the blocking was repeated two more times. The plate was then washed again with three washes of 300ul/well of TBS-Tween. Then
- 30 100ul of Eu-labeled anti-phosphotyrosine antibody diluted to 0.125ug/ml in TBS/Tween containing 0.15mg/ml BSA was added to the wells and allowed to incubate for 30min. with shaking at room temperature. Wells were then washed three times with 300ul of TBS/Tween, 200ul of Enhancement solution was added per well and incubated with shaking for 10min. The plate was then read on the 1420 VICTOR plate counter from

Wallac, Inc. The identical conditions are used for inhibitor studies except that ATP is at 1uM and inhibitors are added, in dimethyl sulfoxide (DMSO) to a final concentration of 1%. Typical concentration ranges in which test compounds are expected to inhibit Myt1 autophosphorylation are 0.001 to 10 uM.

5 **Biological Studies:**

Cell Cycle Studies

Drug studies considering cellular effects were performed in the Hela S3 adherent cell line. Cells were plated at a concentration sufficiently low such that 24 hours later they were at 10-20% confluence (typically 2×10^5 cells/15cm²). Cells were then synchronized in S phase by a repeated thymidine block. Briefly, cells were treated with 2mM thymidine for 18hours, released for 8 hours by 3 washes, and then treated again with thymidine. Following the second release from thymidine, 95% of cells were in S phase. Synchronized cells were then returned to complete media containing a DNA-damaging drug such as 50nM topotecan (a dosage we have found to be sufficient to arrest cells in early G2 phase without inducing apoptosis) alone and in combination with test compounds for up to 18 hours. Cell Cycle profiles were then performed cytometrically using a procedure for propidium iodide staining of nuclei. (Vindelov et al, Cytometry Vol.3, No.5, 1983, 323-327) Myt1 inhibitors would be expected to reverse the G2 arrest caused by the DNA damaging agent. Typical concentration ranges for such activity would be 0.001 to 10 uM.

Proliferation/Apoptosis Studies:

Proliferation studies were performed in a variety of adherent and non-adherent cell lines including Hela S3, HT29, and Jurkat. The proliferation assay utilized a colorimetric change resulting from reduction of the tetrazolium reagent XTT into a formazan product by metabolically active cells (Scudiero et al. Cancer Research, 48, 1981, 4827-4833) Cells were seeded in 100ul in 96 well plates to roughly 10% confluence (cell concentration varied with cell lines) and grown for 24 hours. Compounds were then added with or without sufficient vehicle- containing media to raise the cells to a 200ul final volume containing chemical reagents in 0.2% DMSO. Cells received multiple concentrations of DNA-damaging anti-proliferative drugs such as topotecan, test compounds, and combination treatment at 37°C 5% CO₂. 72 hours later, 50 uls of an XTT/ phenazine methosulfate mixture were added to each well and cells were left to incubate for 90mins. Plate was read at 450nm, and anti-proliferative effects were compared relative to vehicle treated cells. Myt1 inhibitors are expected to inhibit the proliferation of such cancer cell lines and/or enhance the cytotoxicity of DNA-damaging chemotherapeutic drugs. Typical concentration ranges for such activity would be 0.001 to 10 uM. Other assays for cellular proliferation or cytotoxicity could also be used with test compounds, and these assays are known to those skilled in the art.

CDK1 and CDK2

Cyclin dependent protein kinase assays utilized the peptides Biotin-aminohexyl-AAKAKKTPKKAKK and Biotin-aminohexyl-ARRPMSPKKKA-NH₂ as phosphoryl group acceptors. CDK1 and CDK2 were both expressed utilizing a baculovirus expression system and were partially purified to comprise 20-80% of total protein, with no detectable competing reactions present. Typically, assays were performed by incubating either enzyme (0.2-10 nM), with and without inhibitor, one of the two peptide substrates (1-10 nM), [³²P]ATP (1-20 nM), and 10-20 mM Mg²⁺ for periods of time generally within the range 10-120 min. Reactions were terminated with 0.2-2 volumes of either 20% acetic acid or 50-100 mM EDTA buffered to pH 7 (substrate consumption < 20%). The buffer employed in enzyme assays was either 30 mM HEPES 7.4 containing 0.15 M NaCl and 5% DMSO, the buffer 50 mM MOPS 7.0 containing 0.15 M NaCl and 5% DMSO, or the buffer 100 mM HEPES pH 7.5 containing 0.1 mg/mL BSA and 5% DMSO. Inhibitors were diluted in 100% DMSO prior to addition into the assay. Detection of peptide phosphorylation was accomplished by scintillation counting following either collection of peptide onto phosphocellulose filters (for reactions stopped with acetic acid), collection of peptide in wells of 96 well plates coated with Streptavidin (Pierce) (reactions were stopped

- with EDTA), or addition of Avidin coated Scintillant impregnated beads (Scintillation Proximity Assays from Amersham, reactions were stopped with EDTA). Counts detected by any of these methodologies minus the appropriate background (assays with additional 40mM EDTA or lacking peptide substrate) were assumed to be proportional to the reaction
- 5 initial rates, and IC50s were determined by a least squares fit to the equation $CPM = V_{max} * (1 - ([I]/(K + [I]))) + nsb$, or pIC50s were determined by a fit to the equation $CPM = nsb + (V_{max} - nsb) / (1 + (x/10^5 - pIC50))$, where nsb are the background counts.

Tie-2

- The peptide substrate used in the Tie-2 assay was biotin-aminohexyl-
- 10 LEAREYRWLGKKKamide. The kinase domain of the enzyme was purified to homogeneity from a baculovirus expression system. The enzyme was diluted to 10 nM into a 60 μ l reaction containing 100 mM HEPES, pH 7.5, 500 μ M ATP, 10 mM $MgCl_2$, 2 μ M peptide, 1 mM DTT, 0.05 mg/ml BSA, and an inhibitor at varying concentrations. The controls were reactions in the presence (negative controls) or absence (positive controls) of
- 15 50 mM EDTA. Reactions were incubated for 30 min at room temperature, and then quenched by stopped by 80 μ l of 0.15 M EDTA. The quenched samples (125 μ l) were transferred to a Neutravidin plates # 15128 and incubated at room temperature for 30-60 minutes, allowing the biotinylated peptide to bind to the neutravidin on the plates. The neutravidin plates were then washed with water for 5 times. Europium conjugated anti-
- 20 phosphotyrosine antibody, (EG & G Wallac, # CR04-100) (1 mg/ml) was diluted 1:10,000 in 1%BSA-0.05% Tween 20-TBS, and 150 μ l of the diluted antibody was added to each well of the neutravidin plate, so the phosphorylated peptide was bound with the Europium labelled antibody. After another 30-60 min incubation at room temperature, the plates were washed again with water for 5 times. 150 μ l of Enhancemant solution was then added to
- 25 each well, dissociating Eu^{3+} from solid phase bound antibodies to form a homogeneous and highly fluorescent $Eu-(2-NTA)_3(TOPO)_3$ micellar chelate solution. The plates were incubated for 10 minutes at room temperature to allow the above process, and fluorescent signal for each well was determined in a Wallac 1420 Victor Multilabel Counter with "Europium" protocol.
- 30 The kinase activity of all wells was calculated as %S, the percentage of the fluorescent counts vs. positive controls after subtraction of negative controls, as in eq. 1.

$$\% S = 100 * \frac{Counts_{sample} - Counts_{negative}}{Counts_{positive} - Counts_{negative}} \quad (1)$$

35

Plots of compound concentration versus %S were constructed. IC50s (K, expressed in units of molarity), the compound concentration at which the enzyme activity was inhibited by 50%, were determined from nonlinear least squares fits of the data to the simple competitive binding model of eq. 2.

5

$$\%S = \%S_{\max} * (1 - (X / (K + X))) + Y_2 \quad (2)$$

Where %S is the experimentally observed count rate at sample compound concentration X, %S_{max} is the best fit value for the maximum amplitude of the concentration-response curve, Y₂ is the count rate observed at infinitely high inhibitor concentration.

10

CSBP/p38 Kinase:

Compounds capable of inhibiting CSBP/p38 kinase can be identified with in vitro assays and cellular assays as described below. Variations of these assays would be obvious to those skilled in the art.

15

CSBP/p38 Kinase Assay:

This assay measures the CSBP/p38-catalyzed transfer of ³²P from [α-³²P]ATP to threonine residue in an epidermal growth factor receptor (EGFR)-derived peptide (T669) with the following sequence: KRELVEPLTPSGEAPNQALLR (residues 661-681). (See Gallagher *et. al.*, "Regulation of Stress Induced Cytokine Production by Pyridinyl Imidazoles: Inhibition of CSBP Kinase", BioOrganic & Medicinal Chemistry, 1997, 5, 49-64).

20

Reactions were carried in round bottom 96 well plate (from Corning) in a 30 mL volume. Reactions contained (in final concentration): 25 mM Hepes, pH 7.5; 8 mM MgCl₂; 0.17 mM ATP (the K_m[ATP] of p38 (see Lee *et. al.*, Nature 300, n72 pg. 639-746 (Dec. 1994)); 2.5 uCi of [γ-³²P]ATP; 0.2 mM sodium orthovanadate; 1 mM DTT; 0.1% BSA; 10% glycerol; 0.67 mM T669 peptide; and 2-4 nM of yeast-expressed, activated and purified p38. Reactions were initiated by the addition of [γ-³²P]Mg/ATP, and incubated for 25 min. at 37 °C. Inhibitors (dissolved in DMSO) were incubated with the reaction mixture on ice for 30 minutes prior to adding the ³²P-ATP. Final DMSO concentration was 0.16%. Reactions were terminated by adding 10 uL of 0.3 M phosphoric acid, and phosphorylated peptide was isolated from the reactions by capturing it on p81 phosphocellulose filters. Filters were washed with 75 mM phosphoric acids, and incorporated ³²P was quantified using beta scintillation counter. Under these conditions, the specific activity of p38 was 400-450 pmol/pmol enzyme, and the activity was linear for

25

30

up to 2 hours of incubation. The kinase activity values were obtained after subtracting values generated in the absence of substrate which were 10-15% of total values.

PLK-1 assay:

5 An NEN standard flashplate is coated with 1 ug/100 uL/well GST-cdc25c in PBS overnight at 4°C. The plate is washed 2 times with PBS at 250 uL/well and dried 5 to 15 minutes at 37°C. A mixture of 0.5 uCi 33P-ATP and 50 uM ATP are added as 10 uL/well to the dried flashplate. A pre-incubated mixture containing GST-PLK in Kinase Buffer is added as 40 uL/well with a final PLK concentration of 0.5 ug/well (pre-incubation occurs for 1 hour at 37°C). The final volume of 50 uL/well is incubated 1 hour at 37°C at which
10 time the reaction is stopped with 50uL of 50mM EDTA. The plate is washed 4 times with PBS, 300 uL/well, and dried for 30minutes at 37°C. The dried plate is sealed and read on a Topcount using a program designed to read 33P.

Chk1 Kinase Assay:

Each well of a 96 well Flashplate (Amersham, Arlington Heights, VA) was coated
15 with 1ug of the GST-cdc25C fusion protein diluted in PBS. Plates were incubated overnight at 4°C then washed twice in PBS and dried for 5-30 minutes at 37°C. DMSO vehicle or compounds were added as 2uL/well prior to addition of 0.1uCi/well of [³³P]-γATP and 10uM cold ATP and kinase reaction buffer containing 20mM HEPES (pH 7.4), 50 mM KCl, 10 mM MgCl₂, 1 mM EGTA, 0.5 mM DTT. The reaction was initiated by
20 addition of GST-CHK1 (0.5 ug/well) and was allowed to proceed for a time predetermined to be linear on a time vs. phosphorylation plot. Reaction is terminated with the addition of an equal volume (50 uL) of 50-mM EDTA. Plates were washed four times in PBS, dried for 30 minutes at 30°C and quantitated by liquid scintillation counting. Typical concentration ranges in which test compounds are expected to inhibit CHK1 activity are
25 0.001 to 10 uM.

The present invention includes but is not limited to the examples below.

Nuclear magnetic resonance spectra were recorded at 300 MHz using a Bruker AM 300 spectrometer. CDCl₃ is deuteriochloroform, DMSO-d₆ is hexadeuteriodimethylsulfoxide, and CD₃OD is tetradeuteriomethanol. Chemical shifts are
30 reported in parts per million downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, app=apparent, br=broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform

infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical and preparative HPLC were carried out on Rainin or Beckman chromatographs. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. 5 μ Apex-ODS indicates an octadecylsilyl derivatized silica gel chromatographic support having a nominal particle size of 5 μ , made by Jones Chromatography, Littleton, Colorado. YMC ODS-AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada) Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

Following the general procedure described above the following compounds have been synthesized:

Examples:

Example 1

Preparation of 2-[[4-(Diethylamino)butyl]amino]-7-methoxy-6-phenyl-pteridinea) 2-chloro-6-phenyl-pteridin-7-ol

Following the general method of Brown and Mori, Aust. J. Chem. 1985, 38, 467-474, a mixture of 4,5-diamino-2-chloropyrimidine (0.14 g, 1 mmol) and ethyl benzoylformate (0.18 g, 1 mmol) in ethanol (2 mL) was heated to reflux overnight, cooled, filtered, and the filter cake was washed with hexane, and dried to afford the title compound: MS(ES) m/e 259.0 $[M+H]^+$.

b) 2-[[4-(diethylamino)butyl]amino]-6-phenyl-pteridin-7-olA mixture of the compound of Example 1(a) (10 mg, 0.036 mmol) and 4-(diethylamino)butylamine (143 mg, 1 mmol) were heated to 150°C for 1.5 h, cooled, and the mixture purified

by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to give the title compound:
MS(ES) m/e 367.0 [M+H]⁺.

5 c) 7-chloro-2-[[4-(diethylamino)butyl]amino]-6-phenyl-pteridineThe
compound of Example 1(b) is treated with thionyl chloride and a trace of
dimethylformamide in chloroform to give the title compound.

d) 2-[[4-(diethylamino)butyl]amino]-7-methoxy-6-phenyl-pteridineThe
compound of Example 1(c) is treated with sodium methoxide in methanol and
warmed to give the title compound.

10

Example 2

Preparation of 7-[[4-[2-(Diethylamino)ethoxy]phenyl]amino]-2-methoxy-3-phenyl-pyrido[3,4-b]pyrazine

a) 7-chloro-3-phenyl-pyrido[3,4-b]pyrazin-2-ol

15 Following the general method of Bergman et al, Recl. Trav. Chim. Pays-Bas,
1996, 115, 31-36, a mixture of 2-chloro-4,5-diaminopyridine (McCort et al, WO
9842712) and ethyl benzoylformate in ethanol is heated and stirred, and then cooled
and concentrated *in vacuo* to give the title compound.

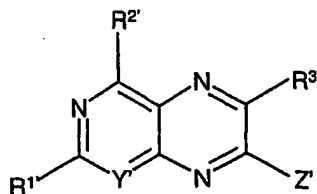
b) 7-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-2-methoxy-3-phenyl-
20 pyrido[3,4-b]pyrazine

Following the procedure of Example 1(b)(c)(d), except substituting the
compound of Example 2(a) for the compound of Example 1(a), gives the title
compound.

25 All publications, including but not limited to patents and patent applications
cited in this specification are herein incorporated by reference as if each individual
publication were specifically and individually indicated to be incorporated by
reference as though fully set forth.

What is claimed is:

1. A compound according to Formula (I), hereinbelow:



(I)

5

wherein:

R¹ is selected from the group consisting of NRR¹, OR, SR, SOR, SO₂R, and halo;

10 R, R¹, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃-10cycloalkyl, C₀-3alkylaryl, C₀-3alkylheterocyclyl, and C₀-3alkylheteroaryl, wherein any of the foregoing carbon containing values may be optionally substituted by one or more of group A, on any position;

15 A is selected from the group consisting of C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃-10cycloalkyl, C₀-3alkylaryl, C₀-3alkylheterocyclyl, C₀-3alkylheteroaryl, C(=NH)R², COR², CONR²R³, CON(O)R²R³, CONR²R³R⁴Y, CO₂R², C(O)SR², C(S)R², cyano, trifluoromethyl, NR²R³, N(O)R²R³, NR²R³R⁴Y, NR²COR², NR²CONR²R³, NR²CON(O)R²R³, NR²CONR²R³R⁴Y, NR²CO₂R², NR²C(O)SR², NR²SO₂R², NR²SO₂NR²R³, nitro, OR², OCF₃,
20 aryloxy, heteroaryloxy, SR², S(O)R², S(O)₂R², SCF₃, S(O)CF₃, S(O)₂CF₃, SO₂NR²R³, SO₃R², PO₃R²R³, and halo, wherein C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃-10cycloalkyl, C₀-3alkylaryl, C₀-3alkylheterocyclyl, (CH₂)₀₋₃heteroaryl, aryloxy, and heteroaryloxy are optionally substituted by one or more of group D, on any position;

25 Y is selected from an inorganic or organic anion;

D is selected from the group consisting of C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃-10cycloalkyl, C₀-3alkylaryl, C₀-3alkylheterocyclyl, C₀-

3alkylheteroaryl, C(=NH)R², COR², CONR²R³, CON(O)R²R³, CONR²R³R⁴Y,
 CO₂R², C(O)SR², C(S)R², cyano, trifluoromethyl, NR²R³, N(O)R²R³,
 NR²R³R⁴Y, NR²COR², NR²CONR²R³, NR²CON(O)R²R³, NR²CONR²R³R⁴Y,
 NR²CO₂R², NR²C(O)SR², NR²SO₂R², NR²SO₂NR²R³, nitro, OR², OCF₃,
 5 aryloxy, heteroaryloxy, SR², S(O)R², S(O)₂R², SCF₃, S(O)CF₃, S(O)₂CF₃,
 SO₂NR²R³, SO₃R², PO₃R²R³, and halo, wherein C₁-galkyl, C₁-galkanoyl, C₂-
 galkenyl, C₂-galkynyl, C₃-10cycloalkyl, C₀-3alkylaryl, C₀-3alkylheterocyclyl, C₀-
 3alkylheteroaryl, aryloxy, and heteroaryloxy may be substituted by one or more of
 E, on any position;

10 R and R¹ together with the nitrogen to which they are attached and R¹⁴ and
 R¹⁵ together with the nitrogen to which they are attached may optionally and
 independently be N=CR²R³ or N=CR²NR²R³, and R¹ and R¹⁵ may optionally and
 independently be [hydrogen,]C(=NH)R², C(=NH)NR²R³, COR², C(S)R²,
 CONR²R³, CO₂R², C(S)NR²R³, SO₂R², SO₂NR²R³, or -[C=N(CH₂)₂₋₄(O)₀₋₁-
 15], and R and R¹ together with the nitrogen to which they are attached and R¹⁴ and
 R¹⁵ together with the nitrogen to which they are attached may optionally and
 independently may form a ring having 3 to 7 carbon atoms, optionally containing 1,
 2, or 3 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur,
 and nitrogen substituted with hydrogen, C₁-galkyl, or (CH₂)₀₋₃aryl;

20 R², R³, and R⁴ are independently selected from the group consisting of
 hydrogen, C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃-10cycloalkyl,
 C₀-3alkylaryl, C₀-3alkylheterocyclyl, and C₀-3alkylheteroaryl; or R² and R³ taken
 together with the nitrogen to which they are attached may optionally form a ring
 having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected
 25 from the group consisting of nitrogen, oxygen, sulfur, and nitrogen substituted with
 hydrogen, C₁-galkyl, or (CH₂)₀₋₃aryl, wherein any of the foregoing carbon
 containing values may be optionally substituted by one or more of group E, on any
 position;

E is selected from the group consisting of C₁-galkyl, C₁-galkanoyl, C₂-
 30 galkenyl, C₂-galkynyl, C₃-10cycloalkyl, C₀-3alkylaryl, C₀-3alkylheterocyclyl, C₀-
 3alkylheteroaryl, C(=NH)R⁵, COR⁵, CONR⁵R⁶, CON(O)R⁵R⁶, CONR⁵R⁶R⁷Y,

CO₂R⁵, C(O)SR⁵, C(S)R⁵, cyano, trifluoromethyl, NR⁵R⁶, N(O)R⁵R⁶,
 NR⁵R⁶R⁷Y, NR⁵COR⁵, NR⁵CONR⁵R⁶, NR⁵CON(O)R⁵R⁶, NR⁵CONR⁵R⁶R⁷Y,
 NR⁵CO₂R⁵, NR⁵C(O)SR⁵, NR⁵SO₂R⁵, NR⁵SO₂NR⁵R⁶, nitro, OR⁵, OCF₃,
 aryloxy, heteroaryloxy, SR⁵, S(O)R⁵, SO₂R⁵, SCF₃, S(O)CF₃, S(O)₂CF₃,
 5 SO₂NR⁵R⁶, SO₃R⁵, PO₃R⁵R⁶, and halo, wherein C₁-galkyl, C₁-galkanoyl, C₂-
 galkenyl, C₂-galkynyl, C₃-10cycloalkyl, C₀-3alkylaryl, C₀-3alkylheterocyclyl, C₀-
 3alkylheteroaryl may be optionally substituted by one or more of a substituent
 selected from the group consisting of C(=NH)R⁵, COR⁵, CONR⁵R⁶,
 CON(O)R⁵R⁶, CONR⁵R⁶R⁷Y, CO₂R⁵, C(O)SR⁵, C(S)R⁵, cyano, trifluoromethyl,
 10 NR⁵R⁶, N(O)R⁵R⁶, NR⁵R⁶R⁷Y, NR⁵COR⁵, NR⁵CONR⁵R⁶, NR⁵CON(O)R⁵R⁶,
 NR⁵CONR⁵R⁶R⁷Y, NR⁵CO₂R⁵, NR⁵C(O)SR⁵, NR⁵SO₂R⁵, NR⁵SO₂NR⁵R⁶,
 nitro, OR⁵, OCF₃, aryloxy, heteroaryloxy, SR⁵, S(O)R⁵, SO₂R⁵, SCF₃, S(O)CF₃,
 S(O)₂CF₃, SO₂NR⁵R⁶, SO₃R⁵, PO₃R⁵R⁶, and halo, on any position;

R⁵, R⁶, and R⁷ are independently selected from the group consisting of
 15 hydrogen, C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃-10cycloalkyl,
 C₀-3alkylaryl, C₀-3alkylheterocyclyl, and C₀-3alkylheteroaryl; or R⁵ and R⁶ taken
 together with the nitrogen to which they are attached may optionally form a ring
 having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected
 from nitrogen, oxygen, sulfur, or nitrogen substituted with hydrogen, C₁-6alkyl or
 20 (CH₂)₀₋₃aryl;

R^{2'} is selected from the group consisting of hydrogen, C₁-galkyl, COR⁸,
 CONR⁸R⁹, CO₂R⁸, cyano, trifluoromethyl, NR⁸R⁹, N(O)R⁸R⁹, NR⁸R⁹R¹⁰Y,
 nitro, OR⁸, OCF₃, SR⁸, S(O)R⁸, S(O)₂R⁸, SCF₃, S(O)CF₃, S(O)₂CF₃,
 SO₂NR⁸R⁹, SO₃R⁸, PO₃R⁸R⁹, and halo;

25 R⁸, R⁹, and R¹⁰ are independently selected from the group consisting of
 hydrogen, C₁-galkyl, C₁-galkanoyl, C₂-galkenyl, C₂-galkynyl, C₃-10cycloalkyl,
 C₀-3alkylaryl, C₀-3alkylheterocyclyl, and C₀-3alkylheteroaryl; or R⁸ and R⁹ taken
 together with the nitrogen to which they are attached may optionally form a ring
 having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected
 30 from nitrogen, oxygen, sulfur, and nitrogen substituted with hydrogen, C₁-galkyl, or
 (CH₂)₀₋₃aryl;

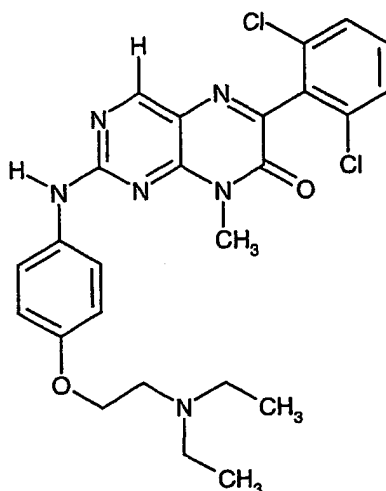
R^{3'} is selected from the group consisting of hydrogen, C₁-galkyl, C₃-gycycloalkyl, aryl and heteroaryl, optionally substituted with one or more of group E, cyano, CONHR¹¹, CONR⁸R⁹, CO₂R⁸, NR⁸R⁹, nitro, OR⁸, or halogen;

- R¹¹ is selected from the group consisting of 2-hydroxyethyl, 2-(C₁-galkoxy)ethyl, or 2-(R¹²R¹³N)ethyl;
- 5 R¹² and R¹³ are independently hydrogen or C₁-galkyl;
- Y' is nitrogen or CR^{2'};
- Z' is NR¹⁴R¹⁵, OH, OR¹⁶, SH, SR¹⁶; S(O)R¹⁶; SO₂R¹⁶, or halo; and
- R¹⁶ is selected from the group consisting of C₁-galkyl, C₂-galkenyl, C₂-galkynyl, C₃₋₁₀cycloalkyl, C₀₋₃alkylaryl, C₀₋₃alkylheterocyclyl, and C₀-galkylheteroaryl, wherein any of the foregoing carbon containing values may be optionally substituted by one or more of group E, on any position.
- 10

2. A compound according to claim 1 wherein:

- 15 R^{1'} is NRR¹;
- R is preferably hydrogen;
- R¹ is C₀₋₃alkylaryl, preferably C₀alkylaryl, more preferably phenyl;
- A is OR²;
- R² is C₁-galkyl, preferably ethyl substituted on the 2-position with E;
- 20 E is NR⁵R⁶, preferably substituted on the 2-position of R² = ethyl;
- R⁵ and R⁶ are independently C₁-galkyl, preferably ethyl;
- R^{2'} is preferably hydrogen;
- R^{3'} is aryl, preferably phenyl, optionally substituted with one or more of group E, wherein E is one or more of C₁-galkyl, trifluoromethyl, or halo, preferably
- 25 dihalo, more preferably 2,6-dichloro;
- Z' is OR¹⁶;
- R¹⁶ is C₁-galkyl, preferably methyl; and
- Y' is nitrogen or CR^{2'}; preferably Y' is nitrogen.

- 30 3. A compound according to claim 2 which is:



4. A compound according to claim 1 selected from the group consisting of:
 6-(2,6-Dichlorophenyl)-2-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-7-methoxy-
 5 pteridine; and
 3-(2,6-Dichlorophenyl)-7-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-2-
 methoxy-pyrido[3,4-b]pyrazine;
 and a pharmaceutically acceptable salt thereof.
- 10 5. A method of antagonizing a Myt1 kinase, Tie2 kinase, or CSBP/p38 kinase
 receptor which comprises administering to a subject in need thereof, an effective amount of
 a compound according to claim 1.
- 15 6. A method according to claim 5 wherein the compound is selected from the group
 consisting of:
 6-(2,6-Dichlorophenyl)-2-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-7-methoxy-
 pteridine; and
 3-(2,6-Dichlorophenyl)-7-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-2-
 methoxy-pyrido[3,4-b]pyrazine;
 20 and a pharmaceutically acceptable salt thereof.

7. A method of treating a disease or disorder selected from the group consisting of leukemias, solid tumor cancers and metastases, soft tissue cancers, brain cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, lung cancer, bladder cancer, bone cancer, prostate cancer, ovarian cancer, cervical cancer, uterine cancer, testicular cancer,
- 5 kidney cancer, head cancer and neck cancer, chronic inflammatory proliferative diseases, proliferative cardiovascular diseases, proliferative ocular disorders and benign hyperproliferative diseases which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1.
- 10 8. A method according to claim 7 wherein the disease or disorder treated is selected from the group consisting of psoriasis, rheumatoid arthritis, diabetic retinopathy and hemangiomas.
9. A pharmaceutical composition comprising a compound according to claim 1 and a
- 15 pharmaceutically acceptable carrier.
10. A method of treating disease characterized by excessive or inappropriate angiogenesis in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound according to claim 1.

20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/08915

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 487/04; A61K 31/4375, 31/4985

US CL : 544/257, 258, 259, 260, 350; 514/249

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/257, 258, 259, 260, 350; 514/249

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/19825 A1 (WARNER-LAMBERT COMPANY) 22 March 2001 (22.03.2001), see formula II, especially page 17, compound no. 4.	1-10
X	US 4,560,685 A (ROCH et al) 24 December 1985 (24.12.85), see Examples A, B and C.	1
X	MERZ, K. et al, Synthesis of 7-Benzylamino-6-chloro-2-piperazino-4-pyrrolidinopteridine and Novel Derivatives Free of Positional isomers. Potent inhibitors of cAMP-specific Phosphodiesterase and of Malignant Tumor Cell Growth, Journal of Medicinal Chemistry, 1998, Vol. 41, No. 24, pages 4733-4743, especially page 4736, compounds in Table 1.	1, 7, 9

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z"

document member of the same patent family

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19 June 2002 (19.06.2002)

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